NDA 21-107

LOTRONEX® (alosetron hydrochloride) Tablets

Selective 5-HT3 antagonist

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

- To mitigate the risk of ischemic colitis (IC) and serious complications of constipation (CoC) associated with LOTRONEX (alosetron hydrochloride) by ensuring that LOTRONEX is used in only severely affected patients for whom benefits exceed the risks.
- To ensure that the risk of IC and serious CoC with the use of LOTRONEX are communicated to patients, pharmacists, and prescribers.

II. REMS ELEMENTS:

A. Medication Guide (MG)

A Medication Guide for LOTRONEX will be dispensed with each LOTRONEX prescription in accordance with 21 CFR 208.24.

A LOTRONEX prescription typically provides the patient with 30-day dosing which is divided into two cartons each containing a bottle with 30 tablets. A copy of the Medication Guide is affixed to each 30-tablet bottle. Copies of the Medication Guide will be available via the lotronexppl.com website or by calling Prometheus Client Services at 1-888-423-5227.

Additionally, as part of the Prescribing Program for LOTRONEX, the LOTRONEX Medication Guide will be provided to certified prescribers who will provide a Medication Guide to each patient at the initiation of each new course of LOTRONEX therapy.

Please see appended Medication Guide.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe LOTRONEX will be specially certified.

a. Prometheus will ensure that healthcare providers who prescribe LOTRONEX are specially certified in the Prescribing Program for LOTRONEX (PPL). To become certified, each prescriber enrolls into the Prescribing Program for LOTRONEX by submitting a completed Prescriber Enrollment Form and attesting to the following:

i. I request to participate in the Prescribing Program for LOTRONEX and acknowledge that I have read and understand the complete Prescribing Information and other enrollment materials for LOTRONEX. I understand the risks associated with its use and will follow the requirements of the Prescribing Program for LOTRONEX described below. I understand the importance of reporting all cases of ischemic colitis and serious complications of constipation to Prometheus at 1-888-423-5227.

ii. I understand that LOTRONEX is approved only for women with severe, diarrhea-predominant irritable bowel syndrome who have:

- chronic irritable bowel syndrome symptoms (generally lasting for 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and
- not responded adequately to conventional therapy.

Diarrhea-predominant irritable bowel syndrome is severe if it includes diarrhea and one or more of the following:

- frequent and severe abdominal pain and discomfort,
- frequent bowel urgency or fecal incontinence,
- disability or restriction of daily activities due to irritable bowel syndrome.

iii. I understand that if I prescribe LOTRONEX for my patient(s), I must be able to perform the following:

- diagnose and manage irritable bowel syndrome, ischemic colitis, constipation, and complications of constipation or refer patients to a specialist as needed.
- ensure that all patients under my care are educated by me or a healthcare provider in my practice about the benefits and risks of the drug.

iv. I agree to:

- provide each of my patients with a copy of the LOTRONEX Medication Guide at initiation of LOTRONEX treatment.
- review the content of the Medication Guide and encourage the patient to read it and ask questions.
- have each patient sign the Patient Acknowledgement Form. The original signed form must be placed in the patient's medical record, and a copy given to the patient.
- inform my patients about the Patient Follow-Up Survey, encourage them to participate and provide them with a Patient Follow-Up Survey Pre-Enrollment Form.
- affix Prescribing Program for LOTRONEX program stickers to written prescriptions for LOTRONEX (i.e., the original and all subsequent prescriptions). Stickers will be provided as part of the Prescribing Program for LOTRONEX. Refills are permitted to be written on prescriptions.
- ensure that all prescriptions for LOTRONEX are written and not transmitted by telephone, facsimile, or computer.

b. PPL Enrollment materials can be requested via the lotronexppl.com website or by phone at 1-888-423-5227.
c. Prometheus will provide prescribers a PPL kit upon their enrollment.
d. Prometheus will maintain a database of all certified enrolled prescribers.

The following materials are part of the REMS and are appended:

- PPL Enrollment Materials
  - Prescriber Enrollment Form
  - PPL Enrollment Letter
  - PPL Prescriber Education Slide Deck
  - Prescribing Information
- LOTRONEXPPL Website For Prescriber Section webshots
- PPL Kit
  - PPL Kit Overview Letter
  - Patient Acknowledgement Form
  - Medication Guide
  - PPL stickers
  - Patient Follow-Up Survey Pre-Enrollment Form
- PPL Sticker Sheet
- Patient Follow-Up Survey Pre-Enrollment Form (included in the LOTRONEX Retail Pack)

2. Each patient prescribed LOTRONEX must have signed a Patient Acknowledgement Form for documentation of safe-use conditions. By signing the Patient Acknowledgement Form the patient agrees to the following:

a. My doctor or healthcare provider under a doctor's direction, answered my questions about treatment with LOTRONEX. I have read and I understand the Medication Guide for LOTRONEX, including the section "Who should not take LOTRONEX?". I understand that about 1 out of every 1,000 women who take LOTRONEX may get serious complications of constipation. I understand that about 3 of every 1,000 women who take LOTRONEX over a 6-month period may get a serious problem where blood flow to parts of the large bowel is reduced (ischemic colitis). I understand that the serious condition of ischemic colitis, and other serious complications of constipation, can happen suddenly. These serious complications may lead to a hospital stay, and in rare cases, blood transfusions, surgery, and death.

b. I understand that certain people may be more likely to develop a serious bowel condition while taking LOTRONEX, including people who:

- are older,
- have other health problems,
- take other medicines that may cause constipation.

c. I understand LOTRONEX is a medicine that should only be used for some women with severe chronic irritable bowel syndrome (IBS), whose main problem is diarrhea, and whose IBS symptoms have not been helped enough by other treatments.

d. I will follow instructions in the Medication Guide about:

- **telling my doctor**, before taking LOTRONEX, about any illnesses I have, or other medicines I am taking or planning to take.
- **taking LOTRONEX** exactly as my doctor prescribes it.
- **stopping LOTRONEX** and calling my doctor right away if I get constipated, if I have new or worse pain in my stomach area (abdomen), or if I see blood in my bowel movements.
- **calling my doctor** again if the constipation I called about before has not gotten better.
- **not starting LOTRONEX again** unless my doctor tells me to do so, if I stopped taking it because I got constipated.
- **talking with my doctor 4 weeks after starting LOTRONEX** to recheck my IBS symptoms.
- **stopping LOTRONEX and calling my doctor** if my IBS symptoms have not improved after 4 weeks of taking 1 mg LOTRONEX 2 times a day.

e. If I see other doctors about my IBS or possible side effects from LOTRONEX, I will tell the doctor who prescribed LOTRONEX .

The following materials are part of the REMS and are appended.

- Patient Acknowledgement Form
- LOTRONEXPPL Website for Patients Section
- LOTRONEX Medication Guide

3. Pharmacists will only dispense LOTRONEX to patients with documentation of safe-use conditions:

a. The pharmacists will only dispense a prescription for LOTRONEX in the presence of a PPL sticker.

- The PPL sticker provides verification to the pharmacist that the prescription is written by a certified prescriber enrolled in the PPL.
- Pharmacists will not accept telephone, facsimile, or computerized prescriptions for LOTRONEX. The prescription may provide refills (30 day supplies).

b. At the time of filling the prescription, pharmacists will dispense to the patient a 30-day supply which includes a copy of the Medication Guide.

c. Prometheus will perform educational mailings twice-a-year (beginning no later than 3 months following the date of approval of this REMS) to pharmacists and retail pharmacies entitled “Important Information for Pharmacists” for a period of 2 years upon approval of the REMS and annually thereafter. The mailings will remind the pharmacists about their role within the PPL.

d. Prometheus will direct pharmacists to review educational materials on the pharmacist section of the LOTRONEXPPL website. The educational materials will consist of a PPL Pharmacist Education Slide Deck [based on the approved PPL Prescriber Education Slide Deck] discussing the benefits and risks of LOTRONEX therapy and the pharmacist role in ensuring compliance with the PPL sticker program.

The following materials are part of the REMS and are appended:

- Educational Mailing: Important Information for Pharmacists
- PPL Pharmacist Education Slide Deck
- LOTRONEXPPL Website For Pharmacists Section webshots

C. Implementation System

The implementation system for the LOTRONEX REMS includes the following:

- Prometheus will monitor compliance with completion of the Prescriber Enrollment Form and Patient Acknowledgement Form to help ensure LOTRONEX is prescribed by PPL-enrolled prescribers and that patients are only treated with LOTRONEX following documentation of safe use conditions by conducting surveys of prescribers and patients.

- Prometheus will monitor compliance with the PPL sticker program by conducting surveys of pharmacists, prescribers, and patients to help ensure LOTRONEX prescriptions are written by PPL-enrolled prescribers and dispensed by pharmacists in accordance with the requirements of the PPL.

- Based on monitoring and evaluation of the elements to assure safe use in section IIB, Prometheus will take reasonable steps to improve the implementation of these elements, if found to be inadequate, and to address non-compliance with the requirements of the PPL.

D. Timetable for Submission of Assessments

Prometheus will submit REMS Assessments to the FDA every 6 months for the first year from the date of approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Prometheus will submit each assessment so that it will be received by the FDA on or before the due date.